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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/533,466	03/23/2000	Frank R. Collart	21416/90042	9908

23644 7590 02/06/2003

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EXAMINER

MARSCHEL, ARDIN H

ART UNIT PAPER NUMBER

1631

DATE MAILED: 02/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/533,466</b>	Applicant(s) <b>Collart et al.</b>
	Examiner <b>Ardin Marschel</b>	Art Unit <b>1631</b>

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1)  Responsive to communication(s) filed on \_\_\_\_\_
- 2a)  This action is FINAL.      2b)  This action is non-final.
- 3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

- 4)  Claim(s) 2-4, 6, 7, and 9-15 is/are pending in the application.
- 4a) Of the above, claim(s) 9-15 is/are withdrawn from consideration.
- 5)  Claim(s) \_\_\_\_\_ is/are allowed.
- 6)  Claim(s) 2-4, 6, and 7 is/are rejected.
- 7)  Claim(s) 1, 5, and 8 have been canceled. ~~is/are objected to~~
- 8)  Claims 2-4, 6, 7, and 9-15 are subject to restriction and/or election requirement.

#### Application Papers

- 9)  The specification is objected to by the Examiner.
- 10)  The drawing(s) filed on \_\_\_\_\_ is/are a)  accepted or b)  objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12)  The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

- 13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some\* c)  None of:

1.  Certified copies of the priority documents have been received.
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

- 14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a)  The translation of the foreign language provisional application has been received.
- 15)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- 1)  Notice of References Cited (PTO-892)
- 2)  Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3)  Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_
- 4)  Interview Summary (PTO-413) Paper No(s). 27
- 5)  Notice of Informal Patent Application (PTO-152)
- 6)  Other: *Attachment for PTO-948*

In order to correct an inadvertent omission of an indication of rejected claims on page 14 of the previous Office action, mailed 1/27/03, the response time is restarted as of the mailing date of this action. The remainder of this action is reiterated from said Office Action, mailed 1/27/03.

Applicants' arguments, filed 6/13/02, have been fully considered and are deemed to be persuasive to overcome previous rejections of record as of said date of 6/13/02. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Upon reconsideration, the following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application.

Due to the newly applied rejections, herein summarized, the finality of the Office Action, mailed 10/15/01, is hereby withdrawn. The amendment, filed 6/13/02, has been entered. The amendments, filed 2/13/02 and 5/6/02, have not been entered. Due to the withdrawal of the finality as noted above, the Notice of Appeal, filed 4/15/02, is deemed moot.

#### DRAWING INFORMALITIES

Applicants are hereby notified that the required timing for the correction of drawings has changed. See the last 6 lines on the sheet which is attached entitled "Attachment for PTO-948 (Rev. 03/01 or earlier)". It is noted that a PTO Form 948 was mailed with Paper No. 20 on 3/27/02. Due to the above

notification Applicants are required to submit drawing corrections within the time period set for responding to this Office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action. This Notice

#### TITLE

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present claims under examination are directed to crystals, crystalline molecules or molecular complexes, and methods of developing lead compounds for inhibition of bacterial IMPDH; whereas, in contrast, the present title is only directed to a use thereof.

#### SCOPE OF ENABLEMENT REJECTION

Claims 2-4, 6, and 7 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for crystals, crystal complex, molecular complex, or methods of use of a IMPDH crystal wherein the crystal is set forth with atomic coordinates limited to those in instant Table 7, does not reasonably provide enablement for any other crystal etc. practice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Applicants have described the expression and subsequent crystallization and analysis of crystalline IMPDH, encoded by *Streptococcus pyogenes* genomic sequence, as summarized in the specification on pages 17-21 with the resultant atomic coordinates listed for select amino acids in Table 7 on pages 26-128. Applicants have not instantly disclosed their performance of the expression, crystallization, and atomic coordinate generation for any other crystal, IMPDH or otherwise. Concerning

the predictability of forming useful crystals, especially for X-ray crystallographic coordinate analysis and generation, the publication of Drenth is hereby cited. In Drenth, Chapter 1, page 1, section entitled "1.2 Principles of Protein Crystallization", the "Obtaining of suitable single crystals is "the least understood step in the X-ray structural analysis of a protein.". Drenth goes on to state that "Protein crystallization is mainly a trial-and-error procedure". Drenth additionally states that "impurities, crystallization nuclei, and unknown factors" play a role in the process. Considering this description the crystallization process is reasonably deemed to be unpredictable and thus lacking in enablement except for crystal preparation which results in the generation of useful atomic coordinates. It is noted that this is specifically required in instant claims 2 but appears only to be instantly disclosed only via the instant disclosure for the crystal which has resulted in the coordinates listed in said Table 7.

#### FURTHER SCOPE OF ENABLEMENT REJECTION

Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling (subject to the above scope of enablement rejection) for methods of developing lead compounds utilizing a IMPDH binding pocket as defined by the amino acids set forth in claims 6 or 7, does not reasonably provide enablement for any other IMPDH binding pocket practice as

included in instant claim 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Applicants have described the binding pocket as defined by the structure coordinates of IMPDH via specific amino acids as listed in claims 6 and 7. No other binding pocket amino acid list has been instantly disclosed. It is noted that comparison

to other enzymes in particular subsections of binding pocket have been described in the specification but that none of these other enzymes have been disclosed as to the entirety of a binding pocket in said other enzymes. In order to define a binding pocket the atomic coordinates of the amino acid atoms surrounding such a pocket must be defined as well as analyzed regarding ligand binding in order to determine which amino acids interact sufficiently with a typical ligand or structurally support or define said pocket so as to be binding pocket amino acids. This multilevel analysis is complex as it is three dimensional as well as requiring typical ligand shape information also. Such complex analysis is deemed undue experimentation without at least having a 3-dimensional structure as a guide. It is noted that only one 3-dimensional structure is instantly disclosed for IMPDH enzyme thus resulting in this lack of enablement rejection for other enzymes and corresponding binding pockets.

#### LACK OF WRITTEN DESCRIPTION REJECTION

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification discloses the amino acids of the IMPDH binding pocket in claims 6 and 7 which corresponds to the

IMPDH encoded by *Streptococcus pyogenes* genomic sequence. This binding pocket set of amino acids meets the written description provision of 35 USC 112, first paragraph. However, claim 4 is directed to encompass any bacterial IMPDH binding pocket structure. None of these non-disclosed binding pockets meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the binding pocket amino acid set in claims 6 or 7, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. , 107

F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the amino acid set as set forth in claims 6 or 7 for the IMPDH binding pocket therein defined, but not the full breadth of claim 4 meets the written description provision of 35 USC 112, first paragraph. Applicants are reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

#### VAGUENESS AND INDEFINITENESS

Claims 2-4, 6, and 7 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 2-4 the phrase "bacterial IMPDH" is present. This phrase has two different interpretations which causes the metes and bounds of the claims to be vague and indefinite. One interpretation is that the IMPDH source is bacterial DNA, for example in a bacterial genome, which is expressed to result in IMPDH enzyme. Another interpretation is that the IMPDH is

expressed in a bacterial host but may be IMPDH which is encoded in another organism's DNA, such as, for example, Hamster or human DNA. It is widely known that the expression of an enzyme commonly undergoes post-translational modification which differs from host organism to host organism of different types. Also the expression of a sequence in a heterologous host cell may result in an inactive protein compared to the protein expressed in its original source cell type. Thus, IMPDH which is expressed in a heterologous bacterial host is expected to differ somewhat as compared to being expressed in the original source organism from which it may be isolated after expression from a genomic sequence. Thus, a possible interpretation of "bacterial IMPDH" is that bacterial expression has resulted in some amount of bacterial character, such as via post-translational modification but is yet encoded by a non-bacterial host cell, or, alternatively, another bacteria type. It is noted that instant claim 3 only specifically defines the bacterial preparation but not the source of the coding sequence from which the IMPDH enzyme is expressed. It is acknowledged that the first interpretation given above is probably the most common interpretation of the cited phrase but that claims are to be interpreted as broadly as reasonable and the second interpretation discussed above is deemed to be sufficiently supported as given in reasoning set forth above. Clarification of the metes and bounds of the

instant claims is requested via clearer claim wording.

It is noted that instant claims 6 and 7 both cite specific amino acids by numbers, such as 50-56 etc. These apparently are number designations which point to corresponding amino acids in the IMPDH enzyme which is encoded by *Streptococcus pyogenes* wherein the entirety of the sequence is 493 amino acids. There confusingly, however, are two different numberings for amino acids of said enzyme as present in the instant application. One numbering is present in Table 7 and another numbering is present in SEQ ID NO: 23. For example, an important amino acid is the Cys310 as discussed in the specification on page 7, line 31. Thus the amino acid residue at position 310 is expected to be Cysteine. Consideration of SEQ ID NO: 23 reveals that position 310 contains a Threonine. SEQ ID NO: 23, however, contains a Cysteine at position 309. However, within Table 7 the listing of atomic coordinates at position 310 is Cysteine. Consideration of the entirety of the instant disclosure confusingly has failed to reveal a complete 493 amino acid sequence for the IMPDH enzyme which is encoded by *Streptococcus pyogenes* which clearly could define the amino acids which correspond to those listed by number in instant claims 6 and 7. The above noted differing numbering of amino acid residues leads to unclarity as to what is meant by the amino acids numbered as in instant claims 6 and 7. Clarification is requested via clearer claim wording as to what

amino acids are specifically meant by the numbering in instant claims 6 and 7.

#### PRIOR ART REJECTIONS

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim 4 is rejected under 35 U.S.C. § 102(b) and (e)(2) as being anticipated by either Wilson et al. (P/N 6,128,582) or Sintchak et al. [Cell 85:921(1996)]

In the abstract Wilson et al. summarizes the crystallization of IMPDH, generation of a 3-dimensional structure for the enzyme,

and its 3-dimensional modeling usage in methods of developing compounds which inhibit IMPDH. The IMPDH qualifies as a bacterial IMPDH because the crystallized enzyme was produced via a bacterial host. See the above rejection under 35 U.S.C. § 112, second paragraph, regarding various optionally unclear interpretations of what is meant by "bacterial" in claim 4. The host cells were defined in column 20, lines 40-67, including elements of enzyme purification. The IMPDH enzyme encoded from the original source being Chinese Hamster is crystallized and X-ray analyzed as described in columns 21-22. Ligand binding, including inhibitor development, to the IMPDH is disclosed in columns 22-24. It is noted that instant claim 4 lacks any limitation as to a specific IMPDH binding pocket type and also lacks a limitation as to what is specifically meant regarding "bacterial" to describe the type of IMPDH practice in claim 4.

Sintchak et al. equivalently to Wilson et al. purifies Chinese Hamster IMPDH grown in a bacterial host. This bacterial host is defined in Sintchak et al. on page 928, right-hand column, in the section entitled "Crystallization and Data Collection" by referring to Fleming et al. (1996) as the source of the sample for crystal preparation. Fleming et al. (1996) is only cited here to establish the bacterial host source of the IMPDH. Fleming et al. (1996) apparently refers to Fleming et al. [Biochemistry 35:6990 (1996)]. On page 6991, lefthand column,

last 6 lines, the bacterial expression of IMPDH is disclosed.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Whitby et al. [Biochemistry 36:10666 (91997), taken in view of Wilson et al. (P/N 6,128,582)].

Whitby et al. describes the preparation of an IMPDH which is encoded originally in the bacteria, *Tritrichomonas foetus*, and also expressed in a bacterial host as described on page 10667, righthand column, first 2 sentences of the section entitled "EXPERIMENTAL PROCEDURES". The remainder of the publication describes X-ray crystal structure determination of the enzyme

including electron density maps etc. which define its 3-dimensional structure. The reference suggests the usage of this information in identifying and design inhibitory compounds in the last sentence of the abstract on page 10666.

Wilson et al. has been described above as describing the 3-dimensional modeling of IMPDH enzyme with the development of inhibitors via the 3-dimensional structure of IMPDH type enzymes developed from X-ray crystallography.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to perform the IMPDH method of developing inhibitors thereto because Wilson et al. describes this process for IMPDH enzymes given the 3-dimensional structure of the IMPDH enzyme. Whitby et al. describes the 3-dimensional structure of IMPDH from a bacterial source both originally, as well as expressed therein, and motivates and suggests the usage of the 3-dimensional date in inhibitor identification and design. This motivation and suggestion in Whitby et al. suggests the usage of equivalent enzyme types such as the IMPDH in Wilson et al. in such inhibitor design to result in a reasonably expectation of success of performing the method of instant claim 4. It is noted that instant claim 4 is not limited as to the type of bacterial IMPDH utilized therein.

The disclosure is objected to because of the following

informalities:

In the specification on page 4, lines 30-31, a structure which is not visible in the electron density maps is indicated as being marked "????". Consideration of Figure 2a has failed to reveal this "????". It is noted that two question marks, each a single "?", are present at a region cited as "missing region" in the polypeptide of Figure 2a, but that Figure 2a lacks a "????" symbol.

In the specification on page 18, line 16, the word "triptych" appears to be misspelled.

In claim 2, line 1, the phrase "by ability" is awkwardly worded and apparently is missing the pronoun "an" therein.

Correction is required.

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703)308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703)308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703)308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

February 5, 2003

*Ardin H. Marschel*  
ARDIN H. MARSCHEL  
PRIMARY EXAMINER